



The role of hematopoietic growth factors in special populations with chronic hepatitis C: Patients with HIV coinfection, end-stage renal disease, or liver transplantation

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■ ABSTRACT

Certain populations with chronic hepatitis C face special challenges in attaining optimal adherence to antiviral therapy, including patients coinfecting with human immunodeficiency virus, patients undergoing dialysis for end-stage renal disease, and liver transplant recipients. These patient groups may stand to gain particular benefit from the expanding use of hematopoietic growth factors to manage the cytopenic effects of antiviral therapy for hepatitis C. This article reviews the rationale, current evidence, and future prospects for the adjunctive use of growth factors in these special populations with hepatitis C.

The challenge of optimizing adherence to therapy for chronic hepatitis C is particularly pronounced in certain patient populations, including patients coinfecting with both human immunodeficiency virus (HIV) and hepatitis C virus (HCV), patients undergoing dialysis for end-stage renal disease (ESRD), and liver transplant recipients. The challenge stems from these populations' heightened risk of adverse effects from therapy, including enhanced susceptibility to hematologic toxicities, since these adverse effects often lead to

dose reductions or premature discontinuation of pegylated interferon alfa (peginterferon) and ribavirin, the current standard of treatment for chronic hepatitis C.

Managing chronic hepatitis C in these groups is made even more difficult by these patients' apparent risk of more rapidly progressive HCV-associated liver disease, which, in the case of patients with ESRD, pertains especially to the period following renal transplantation. Moreover, for at least two of these populations, patients with HIV/HCV coinfection and liver transplant recipients, ample evidence demonstrates impaired response to combination therapy with peginterferon and ribavirin. For patients with ESRD, ribavirin is considered contraindicated because of the risk of severe anemia.

As clinicians attempt to optimize adherence and avoid dose reductions or premature discontinuation of therapy, the use of hematopoietic growth factors has become increasingly widespread for patients with chronic hepatitis C. Consideration of these growth factors is especially warranted in the patient populations mentioned above, in light of the special challenges they face.

■ OVERVIEW OF THERAPY-INDUCED CYTOPENIAS

In the preceding article in this supplement, Ong and Younossi review in detail the hematologic side effects of combination therapy for chronic hepatitis C. Briefly, both the conventional and pegylated forms of interferon suppress hematopoiesis, often resulting in neutropenia, thrombocytopenia, and a mild reduction in hemoglobin. Ribavirin results in a dose-dependent, reversible hemolytic anemia in a significant number of patients, and when it is used in combination with interferon, the anemia is far more pronounced than with interferon alone. All of these cytopenias can be managed with dose reductions or discontinuation of peginterferon or ribavirin, but abundant data suggest that dose reductions decrease the likelihood of response to therapy.

Much interest has focused on the clinical signifi-

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cance of cytopenias induced by therapy for hepatitis C. There is no doubt that reductions in hemoglobin may result in impaired functional capacity, reduced quality of life, and even organ manifestations such as cardiac ischemia. In contrast, many clinicians have come to question the degree to which interferon-induced reductions in neutrophil count truly predispose to infection^{1,2} or to which interferon-induced thrombocytopenia predisposes to bleeding. Consequently, clinicians generally feel that the risk of clinically significant thrombocytopenia is very low and that reduced platelet counts are the least common hematologic indication for dose reduction or discontinuation. Nevertheless, all clinicians agree on the need to monitor cell counts during therapy and to react to cytopenias of sufficient severity.

■ HEMATOPOIETIC GROWTH FACTORS: RATIONALE FOR THEIR USE IN SPECIAL POPULATIONS

Recombinant erythropoietin and recombinant granulocyte colony-stimulating factor (G-CSF) have garnered interest as potential tools for limiting hematologic side effects—*anemia* and *neutropenia*, respectively—in patients with chronic hepatitis C who are treated with peginterferon and ribavirin. Recombinant erythropoietin has been used successfully in the management of anemia associated with chemotherapy, chronic renal failure, zidovudine therapy for HIV infection, and surgery.³ G-CSF has been used principally in the management of neutropenia associated with chemotherapy.⁴

Increasing evidence suggests that recombinant erythropoietin⁵⁻⁹ and G-CSF⁹⁻¹² may be used safely in patients treated with peginterferon and ribavirin and may potentially minimize the need for dose reductions or discontinuation of therapy, as well as improve adherence to therapy and quality of life. This may be of greatest importance in patients who face the prospect of rapidly progressive liver fibrosis and in whom hematologic side effects are common, including patients with HIV/HCV coinfection, patients with ESRD undergoing dialysis, and liver transplant recipients. However, the use of hematopoietic growth factors has not been adequately evaluated in these patients and further studies will be needed to determine the appropriate dosing and timing of therapy. Of particular note is the absence of firm data from randomized trials showing that hematopoietic growth factor use results in increased rates of sustained virologic response (SVR).

■ PATIENTS COINFECTED WITH HIV

Approximately one third of HIV-infected individuals are also infected with HCV.^{13,14} Patients coinfect

with HIV and HCV are at particular risk of developing anemia and neutropenia during therapy with peginterferon and ribavirin, as they may have underlying HIV-associated hematopoietic dysfunction.¹⁵ Although adherence analyses analogous to those from the large trials in patients infected only with HCV have not yet been presented, the need to provide an optimal course of therapy for HIV/HCV-coinfecting patients should be stressed since these patients have higher serum HCV RNA levels, accelerated fibrosis, a higher prevalence of cirrhosis, higher mortality, and lower rates of virologic response to therapy compared with patients infected with HCV alone.¹⁶

Hematopoietic dysfunction in HIV-infected patients is well described and is likely multifactorial, resulting from direct suppression of progenitor cells by HIV, abnormal cytokine production, medications, opportunistic infection, malignancy, autoantibody production, and the stage of HIV infection.^{15,17}

Anemia: A potential role for erythropoietin

Recombinant erythropoietin has been used widely in the management of HIV-infected patients, particularly in association with zidovudine therapy, which may result in bone marrow suppression and anemia, especially at the higher doses that were common before the advent of highly active antiretroviral therapy.¹⁸ In recent reports of HIV/HCV-coinfecting patients treated with either nonpegylated or pegylated interferon and ribavirin, mean hemoglobin levels fell by as much as 2.3 g/dL¹⁹⁻²³ and 3.5 g/dL,²⁴ respectively, during the first 12 to 24 weeks of therapy, similar to the reductions seen in patients infected with HCV alone.

Preliminary studies suggest that, as in patients infected with HCV alone, recombinant erythropoietin may play a significant role in managing anemia during interferon/ribavirin therapy in patients coinfecting with HIV and HCV.^{24,25} In one study evaluating the use of interferon alfa-2b and ribavirin in 24 coinfecting patients,²⁵ hemoglobin decreased to less than 10 g/dL in 21% of patients. These patients were then treated with recombinant erythropoietin, and their mean hemoglobin level increased to 12.7 g/dL after 4 weeks, although 1 patient was unable to continue therapy because of persistent anemia. Another study,²⁴ still ongoing, is comparing the use of recombinant erythropoietin with ribavirin dose reduction in coinfecting patients who develop anemia during therapy with peginterferon alfa-2b and ribavirin. Patients who received recombinant erythropoietin have demonstrated increases in hemoglobin similar to those achieved by ribavirin dose reduction. These

findings suggest that the use of recombinant erythropoietin in coinfecting patients may improve our ability to continue ribavirin therapy at optimal doses in the setting of ribavirin-induced anemia.

Neutropenia: Preliminary evidence for a role for G-CSF

An important concern when treating patients coinfecting with HIV and HCV is the risk of interferon-associated neutropenia and lymphopenia, which could result in decreased CD4⁺ T-cell counts and potentially an increased risk of opportunistic infections. Lymphocytes may be reduced in up to 14% of patients infected with HCV alone who are treated with peginterferon and ribavirin.²⁶ Preliminary results indicate that CD4⁺ T-cell counts may decrease in HIV/HCV-coinfecting patients treated with either nonpegylated or pegylated interferon combined with ribavirin.^{19,21,23,27} However, the relative proportion of CD4⁺ T cells among total lymphocytes remains unchanged, the significance of which has yet to be established.

As a result of this potential risk, a CD4⁺ T-cell count of less than 100 cells/mL is a relative contraindication to interferon use, as interferon-induced decreases to this level have resulted in AIDS-defining opportunistic infections.²⁸ In coinfecting patients with CD4⁺ T-cell counts below 100 cells/mL, antiretroviral treatment should be prioritized in order to improve CD4⁺ T-cell counts before interferon is prescribed.²⁹ In coinfecting patients with normal CD4⁺ T-cell counts, the question of which disease to treat initially has not been resolved.

The use of G-CSF in HIV-infected patients has been shown to be effective and well tolerated.^{30,31} In patients coinfecting with HIV and HCV, preliminary findings suggest that G-CSF may be as effective as peginterferon dose reduction for the management of interferon-induced neutropenia.²⁴ Although these results appear promising for our ability to avoid potential dose reductions or discontinuation of peginterferon in coinfecting patients, further long-term studies will be required to validate them.

■ PATIENTS RECEIVING DIALYSIS FOR ESRD: ANEMIA IS THE CHIEF CONCERN

Chronic hepatitis C is a frequent problem in patients with ESRD, as 8% to 10% of hemodialysis patients in the United States have been exposed to HCV.^{32,33} Studies suggest that chronic hepatitis C is often relatively quiescent in ESRD patients,³³ but disease progression may accelerate after renal transplantation,³⁴ probably because of the immunosuppressive medications required. Overall, HCV-positive patients undergoing dialysis have higher mortality than HCV-nega-

tive ESRD patients,³⁵ and renal transplantation is beneficial in these patients. Thus, mild chronic hepatitis C is not a contraindication to transplantation.³⁶ Unfortunately, HCV infection is difficult to treat in patients after renal transplantation because of a substantial risk of graft rejection,³⁷ which makes clearance of HCV before renal transplantation highly desirable.

Ribavirin not recommended, interferon not well tolerated

Treatment of chronic hepatitis C in patients with ESRD is particularly challenging because ribavirin is considered contraindicated and because these patients have a reduced tolerance for interferon therapy.³³

Because ribavirin is cleared via renal excretion and only a small fraction is removed by dialysis, patients undergoing dialysis who are treated with ribavirin are at increased risk of severe hemolysis.³⁸ One recent study suggested that ribavirin may be given safely to these patients in low doses (< 300 mg/d).³⁹ In this study, patients received careful follow-up, monitoring of plasma ribavirin levels, and high-dose recombinant erythropoietin before and during therapy. Further studies of this nature will be required to enhance clinicians' confidence in the use of ribavirin in dialysis patients.

Because of the concerns about anemia, most studies in this population have used interferon alone, usually at a dose of 3 million units three times a week. Pharmacokinetic studies have shown that dialysis patients have higher peak and more sustained serum interferon levels than patients with normal renal function.⁴⁰ A meta-analysis of published trials that used interferon 3 million units three times a week demonstrated a higher rate of SVR in HCV-infected patients undergoing dialysis (33%)⁴¹ than was reported previously in large trials among patients with normal renal function who received interferon monotherapy (13% to 19%).^{42,43} At the same time, the incidence of adverse effects appears to be somewhat higher in patients undergoing dialysis. In HCV-infected patients with ESRD, interferon therapy should be strongly considered before renal transplantation, as evidence suggests that renal transplant recipients are at risk of having a severe, accelerated course of HCV-associated liver disease following transplantation while on immunosuppressants.³⁴

Anemia associated with renal failure occurs in virtually all patients with ESRD because of deficient renal production of erythropoietin. As a result, recombinant erythropoietin is widely used to treat anemia in patients with ESRD. Ribavirin is currently considered investigational for patients undergoing hemodialysis and cannot be recommended in routine practice. Whether the aggressive use of recombinant erythro-

poietin can allow for the safe use of ribavirin has yet to be demonstrated in controlled clinical trials.

Although anemia predominates as the major challenge facing dialysis patients receiving antiviral therapy for HCV infection, the usual precautions about reductions in the absolute neutrophil count and platelet count also apply.

■ LIVER TRANSPLANT RECIPIENTS: RECURRENT INFECTION IS COMMON, OFTEN SEVERE

HCV-associated liver disease is the leading indication for liver transplantation in the United States.⁴⁴ In liver transplant recipients who had chronic hepatitis C before transplantation, reinfection with HCV following transplantation is almost universal, and these patients are at risk of a severe, accelerated course of HCV-associated graft disease. In addition, recurrent chronic infection with HCV results in decreased patient and graft survival,⁴⁵ and the severity of recurrent liver disease is associated with the degree of immunosuppression required after transplantation.⁴⁶

The treatment of patients with recurrent HCV infection following liver transplantation is an area of great interest. Many concerns arise over the tolerability and efficacy of therapy with interferon/peginterferon and ribavirin in this population, as well as over the potential for graft rejection during therapy. Unfortunately, interferon monotherapy has shown minimal efficacy in transplant recipients with recurrent chronic hepatitis C, yielding SVR rates of less than 5%.^{47,48} Improved response rates have been observed with the combination of interferon and ribavirin, but efficacy is still poor compared with that in nontransplant patients. One recent study, for example, demonstrated SVR in 21% of liver transplant recipients with recurrent chronic hepatitis C treated with interferon and ribavirin.⁴⁹ In this study, 43% of patients discontinued therapy because of ribavirin-associated hemolytic anemia, and only dose reductions or discontinuation of treatment were used to manage adverse events. Others have observed similarly high rates of anemia in this population.⁵⁰⁻⁵²

The increase in ribavirin-associated hemolytic anemia in these patients may be associated with impaired renal function. Thus, ribavirin dosing in this population may need to be adjusted on the basis of weight and renal clearance to avoid dose reductions or discontinuation.⁴⁹

Preliminary results from a randomized trial in liver transplant recipients with recurrent HCV infection who were treated with peginterferon and ribavirin indicate that larger decreases in hemoglobin were associated with reduced renal clearance, suggesting

that preemptive therapy with recombinant erythropoietin may be important in maintaining adequate doses of ribavirin in these patients.⁵³ Additional studies using hematopoietic growth factors in liver transplant recipients will be required to determine any further benefit in adherence to and tolerance of therapy with interferon/peginterferon and ribavirin.

■ CONCLUSIONS AND IMPLICATIONS FOR THE FUTURE

Hematopoietic growth factors may offer a number of benefits to patients with chronic hepatitis C who are being treated with the combination of pegylated or nonpegylated interferon and ribavirin. These include improved tolerability of and adherence to combination therapy, a higher likelihood of completing a full course of therapy with minimal dose reductions, improved quality of life, and, potentially, prevention of infections. Growth factors may be of particular benefit in patient populations with impaired tolerability of combination therapy and complex treatment issues. Further studies will be required to validate the potential benefits of recombinant erythropoietin and G-CSF in these special populations and in all patients with chronic hepatitis C. It is likely that recombinant erythropoietin will be commonly used in these special populations and that recombinant G-CSF will have more limited use but still have a role in selected patients with severe neutropenia. A number of questions surrounding the use of growth factors have yet to be fully evaluated, including appropriate dosage, time of initiation, duration of therapy, impact on SVR, and cost-effectiveness.

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